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Gamma Globulin

Status of Availability for Prevention of Poliomyelitis

WILTON L. HALVERSON, M.D., and
ROBERT M. DRAKE, M.D., *San Francisco*

• A limited and temporary preventive effect has been noted for gamma globulin used under certain conditions. There is available a supply of gamma globulin which is inadequate to meet the demand with the methods of use indicated in the light of present knowledge.

All supplies of gamma globulin have been placed under the responsibility of the Office of Defense Mobilization. Supplies allocated to the state of California are being made available to physicians through their local health departments on the basis of past and current incidence of poliomyelitis for use in protecting persons in household contact with patients with diagnosed cases. The most effective use of California's allocation of this material can be expected to prevent or modify approximately 40 cases on the basis of the past five-year experience (1947-1951). Parents, physicians and health officials must know the facts and cooperate to make the best of a difficult situation.

THIS SUMMER parents, physicians, and health departments will be concerned about the availability of gamma globulin for use in the prevention of poliomyelitis. With the intense interest that will undoubtedly develop, it seems timely to review the available facts about gamma globulin and its effectiveness, the possible methods for use, the available amounts, and the plans of interested and responsible groups at national, state, and local levels to use a scarce material in the most fair and effective manner.

Since the major impetus to the use of gamma globulin resulted from the field trials reported by Hammon and co-workers,[7,8,9,10] it would seem desirable to summarize their methods of study and the available results, and to note the features as yet unpublished which may be of crucial importance in the final evaluation of the role of gamma globulin in prevention of poliomyelitis.

Specific criteria and controls were used, in an attempt to avoid mistakes due to biased observations or chance variation. These included: (1) Assuring statistically significant results by including a sufficient number of participants. (2) A randomized procedure for injecting all volunteers, half receiving gamma globulin and half receiving gelatin, without anyone's knowing (until evaluation was completed) which subjects received which material. (3) Final analyses based only on paralytic cases.

To obtain sufficient numbers of cases, areas were selected which were experiencing severe epidemics and, furthermore, which had a large enough population to allow a sufficient duration of the epidemic

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Dr. Halverson is Director and Dr. Drake is Medical Officer of the California State Department of Public Health.

to evaluate this temporary immunizing agent. Populations of 50,000 to 100,000 were found best suited for this purpose. Three areas were selected where there were unusually high rates. In the Provo and the Sioux City studies, the annual morbidity rates, respectively, were 160 and 427 per 100,000 population for all ages. At Houston, the rate for that city and county was 82 per 100,000 population.

Injections were given to children in the age group 1 to 11 years. In all, approximately 55,000 children received injections—half with each material. One hundred and four cases occurred in the study group following these injections. Thirty-one occurred in those receiving gamma globulin and 73 in those receiving gelatin. No significant difference between the two groups was noted in the number of cases developing in the first week after injections (12 in the gamma globulin group, 16 in the gelatin group.) A marked difference was noted between the two groups in the second week (3 in the gamma globulin group and 24 in the gelatin group). The difference persisted through the fifth week after injection but the numbers were increasingly smaller. There was a suggestion of protection in a smaller proportion of children in the sixth through the eighth week after injection.

In addition to the evidence for prevention, in those cases occurring within one week after injection of gamma globulin, there were indications that the severity of the disease was significantly modified.

For the three study areas the average ratio of effectiveness was approximately 2 cases prevented or modified per 1,000 persons who received the injection. This ranged from a low of 0.8 cases per 1,000 in Houston to over over 4 cases per 1,000 who received the injection in the Sioux City area.

In addition to the clinical studies, blood and stool specimens were obtained and epidemiologic data collected. The findings based on these data have not yet been reported. Nonetheless, they may give information indicating whether gamma globulin interferes with natural infections which lead to subsequent immunity. This feature, and additional epidemiologic evidence now being analyzed, are of importance in establishing the eventual role of gamma globulin in this disease.

With the reports emanating from the Hammon studies, concern developed that the demands for gamma globulin would exceed the available supply for the summer of 1953. The Office of Defense Mobilization is the national allocating authority for this material. The total available supply from the various sources has been estimated to be about 6 to 7 million cubic centimeters of gamma globulin by July 1, 1953, which is less than 1 million average doses (0.14 cc. per pound of body weight).

A number of factors limit the value of gamma globulin. It gave only temporary protection in the groups studied by Hammon and not all persons inoculated were protected. (For example, during the week of greatest protection 10 per cent of the cases occurred in those inoculated with gamma globulin.[12]) There is no practical way of determining what person is susceptible or, conversely, immune. There is incomplete information as to what constitutes an effective exposure and there is usually uncertainty as to the time the individual is exposed. Furthermore, it is estimated that there is only one recognized case per 100 or more infections. Yet these undiagnosed infections may well serve as a source of virus. If there were methods for ascertaining easily some of the above unknowns, the available supply of gamma globulin might be adequate. However, with the lack of clear-cut indications for use, it appears that the available supply will be inadequate to meet the demand. Thus, it was necessary to establish some "ground rules," so to speak, so as to insure that the supply will be used in the most effective way for all persons concerned.

Among various proposals, two methods have received the most consideration. Each may be considered complementary to the other. The first is the mass community approach of injecting individuals of the most susceptible ages in areas experiencing severe epidemics. This was the method used by Hammon and co-workers. Advantages and disadvantages of this method have been summarized as follows:[4]

"1. The efficacy of the method has been demonstrated in critical tests to prevent or modify on the order of two cases of paralytic illness by the inoculation of 1,000 children in selected age groups.

"2. By this method, an effort may be made to authoritatively restrict the use of a scarce substance to those individuals and locales where maximum benefit may be obtained.

"On the other hand: (1) Mass use requires advance prediction of areas where high attack rates may be anticipated and such prediction is exceedingly difficult. (2) Mass use is decreasingly efficient as the total attack rate decreases, it is decreasingly efficient in very sharp or very prolonged outbreaks, it is decreasingly effective as use is extended into those age groups at lower risk of illness. (3) To achieve results comparable to those of the field experiments would require the maintenance of a highly organized central body with the authority to make prompt and final decisions, to thoroughly evaluate individual situations in which mass prophylaxis may be employed. (4) With the present estimate of the supply of gamma globulin which will be available in 1953, relatively few and scattered areas would receive allotments for mass pro-

phylaxis. Nevertheless, requests for such allotments would be many and would engender a variety of disconcerting pressures on the allocating body."

A second method involves giving gamma globulin to persons who have been in contact with patients known to have the disease. There is epidemiologic evidence that members of a household or family are at a definitely increased risk of developing recognized illness than are the general public.[4, 10] Table 1 presents an estimate of the numbers involved, the important time relationships, and the degree of possible prophylaxis. Unpublished data collected in California in recent years are in general accordance with these estimates.[3]

Of 1,000 paralytic cases, approximately 50 cases will occur in families secondary to an initial case. Of these, 30 will occur simultaneously or so soon after the onset of the first case that no effect from use of gamma globulin can be expected. Fifteen cases will occur from 6 to 12 days after the first case. These cases may be modified. Only five cases can perhaps be prevented. This appears to be a small effect, but Hammon stated that the results obtained should be equal to or better than those resulting from mass prophylaxis except in severe community epidemics.[10]

In addition to the effectiveness noted, other advantages would appear to exist in using a method related to household contacts. These would include: (1) Distribution of gamma globulin can be made equitable and related to the occurrence of cases during the current season. (2) Distribution of gamma globulin may be carried out through already established administrative channels. (3) Criteria for use of gamma globulin in household contacts are relatively easily defined. (4) Use for household contacts requires a relatively small share of the estimated available supply—leaving some available for other categories of use.[4]

TABLE 1.—*Estimated number of secondary cases in households per 1,000 cases of paralytic poliomyelitis by interval between cases and degree of prophylaxis

Days Interval Betweeen Index and Secondary Cases	Number of Secondary Cases Per Thousand Paralytic Cases	Per Cent Secondary Cases	Degree of Possible Prophylaxis
0- 5 days	30	60	None
6-12 days	15	30	Modification
13-30 days	5	10	Prevention
Total.....	50	100	

*See references 10 and 12.

NATIONAL PLANS

On April 15, 1953, a national plan for the allocation of gamma globulin was issued. Of the available supply, 57 per cent is allocated to states and territories on the basis of past and current experience. Thirty-three per cent is held for mass community use in severe epidemic areas, and 10 per cent is kept as a national reserve for unusual or special situations. The state health officer is responsible for the distribution and modes of use of the portion allocated to each state.

ESSENTIAL ELEMENTS OF THE STATE PLAN

An Advisory Committee was appointed by the California State Board of Health, with representation from the state medical and osteopathic associations, the Conference of Local Health Officers, and technical experts, to assist the Director of Public Health in developing a plan for California. After reviewing the available evidence, the Advisory Committee recommended a plan with two basic premises: First, that the national recommendations be accepted, and second, that the state plan be as specific as possible so as to allow the most effective use of a limited material on a statewide basis.

Ninety per cent of this basic allotment to the state will be distributed to cities and counties on the basis of past and current incidence. A state reserve of 10 per cent will be established for unusual and emergency situations.

Of the 90 per cent portion, one-third will be sent to each city and county where full-time public health departments exist and to the county health officer of counties without full-time health departments. Additional amounts may be had upon request of the local health officer in accordance with the current incidence of the disease in that area. Should additional supplies in excess of the state's basic allotment be received, they will be apportioned to those areas experiencing an increased incidence over the five-year mean (1947-51).

The material is to be available for use in selected household contacts of diagnosed cases. These contacts are those persons 30 years or under and pregnant women of any age. The following features were considered in selecting these criteria:

1. Household contacts of a known case have a greater risk of developing poliomyelitis than the general public.[4, 10]

2. Studies of virus distribution in communities show a concentration in households where cases develop.[6]

3. Ninety per cent of reported cases of poliomyelitis in California for the last five years occurred in the age group under 30 years. Only 10 per cent of the cases occurred in the older age groups which include one-half of the state's population.

4. Pregnant women are at an increased risk of having the disease.[1]

Information to be required from the physician for the obtaining of gamma globulin includes the identification of the case (name, age, sex and address of the patient, the date of onset, and type of disease) and the names, ages, and weights of eligible contacts.

The exact methods of collecting records and distributing gamma globulin will be determined in each local area. It is recommended that physicians and health officers work out these arrangements together. Health officers have agreed that in areas with several health departments serving overlapping population and physician concentrations, methods will be developed to assure the maximum convenience to the physicians and people affected.

A local health officer may send a request through the state health officer for a supply to undertake a mass prophylaxis in the event of a severe epidemic. After investigation and on the recommendation of the State Advisory Committee, this request may be forwarded to the Office of Defense Mobilization. Criteria are being developed nationally for the determination of when an area becomes eligible for such use of gamma globulin.

What can be expected of these methods as applied to California this year? For purpose of illustration, let us consider that California will have an average year of 3,000 cases, and will receive approximately 180,000 cubic centimeters of gamma globulin (18,000 average doses). If California used its entire supply for mass community prophylaxis under conditions as suitable as those reported by Hammon and co-workers, approximately 36 cases of poliomyelitis may be prevented or modified out of the 3,000 cases. Recent California experience, however, makes it seem unlikely that a situation meeting the proposed criteria for mass prophylaxis will ocur. Hammon does not recommend mass community prophylaxis unless an area experiences an annual morbidity rate of 160 or more per 100,000 population for all ages.[10] In the past five years, no county in California has experienced such rates (see Table 2). This discussion is limited to the past five years, since the pattern of incidence appears to have changed from a low endemic pattern with recurrent epidemics to a higher endemic level (see Table 3). As to California cities in the population range from 15,000 to 51,000 (the national plan suggests that cities in this range are the most likely to experience these severe epidemics), it is noted that only six outbreaks with rates over 160 per 100,000 occurred in cities of this size in the past five years (see Table 4). All six occurred in cities which are in metropolitan areas, and for that reason it might be difficult administratively or scientifically to justify selecting such areas for mass community prophylaxis in preference to contiguous areas.

According to Hammon and co-workers, family or household contact prophylaxis after the diagnosis of a case should produce benefits equal to or better than those produced by the mass community methods in all areas except those of the most severe epidemics.[10] Based on an average year in California of 3,000 cases, of which about 70 per cent are paralytic, it is estimated that approximately 40 cases of paralytic poliomyelitis could be modified or prevented by this method. This is essentially the same as would obtain using the mass community technique under the circumstances described by Hammon.

TABLE 3.—*Reported cases of poliomyelitis and case rates—California, 1940-52

Year (Calendar)	Population† July 1 Estimated	Reported Cases	Rate per 100,000
1940 Census	6,980,000	440	6.3
1941 Estimated	7,306,000	237	3.2
1942 Estimated	7,859,000	365	4.6
1943 Estimated	8,428,000	2,655	31.5
1944 Estimated	8,832,000	428	4.8
1945 Estimated	9,148,000	950	10.4
1946 Estimated	9,548,000	2,239	23.4
1947 Estimated	9,864,000	735	7.4
1948 Estimated	10,165,000	6,070	59.7
1949 Estimated	10,434,000	2,623	25.1
1950 Census	10,634,000	2,313	21.7
1951 Estimated	11,100,000	3,198	28.8
1952 Estimated	11,460,000	4,047	35.3

*Source: Morbidity Records, Bureau of Acute Communicable Diseases, California State Department of Public Health.

†Estimates of State Department of Finance—November 1951, p. 14, prepared by Carl M. Frisen.

TABLE 2.—*Poliomyelitis—annual cases per 100,000 population in counties of California, 1948-1952 inclusive*

County Population in Thousands	Number of Counties	Total County Years	Case Rates per 100,000 Population: 150+	100-149	75-99	50-74	30-49	15-29	1-14	Too Few for Rates	No Cases
500+	4	20	....	....	1	1	5	10	3	....	....
200-299*	9	45	....	1	1	....	22	21	....	....	....
100-199	7	35	....	....	....	4	12	14	5	....	....
50- 99	8	40	....	2	3	6	7	16	6	....	....
15- 49	15	75	....	2	3	3	17	24	13	9	4
Less than 15	15	75	....	1	5	3	7	9	1	23	26
Total	58	290	....	6	13	17	70	94	28	32	30

*There are no counties with populations between 300 and 500 thousand.

TABLE 4. — *Poliomyelitis—annual case rates per 100,000 in selected cities of 15-51 thousand population, 1948-1952 inclusive*

City Population in Thousands	Number of Cities	Total City Years	Case Rates per 100,000 Population								
			150+	100-149	75-99	50-74	30-49	15-29	1-14	Too Few for Rates	No Cases
45-51	6	30	....	3	....	4	9	11	3	....	....
35-44	3	15	....	1	....	1	8	1	4	....	....
25-34	9	45	....	3	6	4	13	10	7	2	....
20-24	12	60	3	2	1	15	14	14	6	1	4
15-19	17	85	3	1	8	13	23	25	6	5	1
Total	47	235	6	10	15	37	67	61	26	8	5

With the state plan as adopted, California should benefit from both of these methods. The basic allotment of 180,000 cubic centimeters is to be used for household contacts of persons with diagnosed cases. If suitable epidemics develop, a request can be made for gamma globulin for mass community prophylaxis. As will be noted, the total net effect from either method or both, with the available supplies, will be very small. Only 1 to 2 per cent of all reported cases in the state will be affected by either of these methods. That is to say, on the basis of present information, there will be no effect on the bulk (98 per cent or more) of the reported cases of poliomyelitis in the state.

In using the household contact method, two dilemmas arise at once. First, a rigid definition of "household contact," although it seems necessary to conserve a scarce material for use in a population at definitely increased risk, may sometimes work hardship in a particular situation. Nonetheless, it was felt by the State Advisory Committee that if gamma globulin were used for non-household contacts (and where would the line be drawn among this group?) not only would the supply be quickly exhausted without obtaining any effective results, but the possibility of getting additional data on the effectiveness of this method would be spoiled. Second, the establishment of a diagnosis of non-paralytic poliomyelitis may present difficulties. Especially this is so in the areas where the arthropod-borne encephalitides are endemic.

"There is one subjective disadvantage which should not be overlooked," it was pointed out in a report by the National Research Council.[12] "Some 60 per cent of secondary family cases will be neither prevented nor modified by the use of gamma globulin [since 60 per cent of cases occur within 0 to 5 days of the first case]. Unless physicians and the public are fully informed of this situation, an unjustifiably critical attitude toward the value of gamma globulin may develop. The public will see the failures of prophylaxis; the successes will be hidden from it."

Health officers and private physicians are together confronted with an unusually difficult problem. Not only is gamma globulin in very short supply but in spite of its limitations the public has been led to believe that it is an effective preventive for poliomyelitis. Health officers must therefore work closely with physicians in private practice and constantly keep the people of California informed on the facts regarding gamma globulin and the current incidence of poliomyelitis.

760 Market Street.

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